

ORAL PENICILLIN FOR GONORRHOEA*†

SOME EXPERIENCES WITH PHENOXYMETHYL PENICILLIN (PENICILLIN V) IN WHITE AND NEGRO PATIENTS

BY

R. R. WILLCOX

St. Mary's Hospital, Paddington, London

The greater simplicity of treating gonorrhoea with penicillin given orally rather than by injection has, other things being equal, a number of administrative advantages. On the other hand, too simple a treatment may lead to slipshod work by relatively unqualified persons with inadequate diagnostic control.

When penicillin was introduced it was considered that its rapid destruction in the stomach would prevent its use by the oral route. It was soon shown however, that the destruction was not complete and that curative treatments could be given by using an appropriately higher dose. The calcium salt was used at first and the tablets were buffered to combat the stomach acid.

Bushby and Harkness (1946) gave six doses of only 40,000 units to 62 patients, prescribing potassium citrate and restricting fluid. The majority were followed-up for 6 months and only two failures and one case of epididymitis were noted. Ross, Burke, and Olansky (1947) cured 57 of 63 adults with acute gonorrhoea (90.5 per cent.) by giving 50,000 units every 3 hrs. for six doses. Porudemiskii and Zalutskii (1948), who treated 97 cases, including 73 cases of sulphonamide-resistant gonorrhoea, with only 200,000–300,000 units given orally, claimed 79 cures (81.4 per cent.).

Using buffered tablets, Robinson (1950) and Jacoby and Ollswang (1950) had 80–87 per cent. of cures in males with gonorrhoea given 250,000–600,000 units orally. The latter workers gave four doses of 100,000 units at hourly intervals. Horne (1950) gave 500,000 units of calcium penicillin orally, repeating the dose 3 to 6 hrs later, and had only three failures in fifty patients treated. Besides buffering, other trials were made of penicillin incorporated in a mixture of lanoline and sesame oil, or in cocoa butter, or in the form of enteric-coated capsules (*e.g.* Seager, Shoemaker, Mulholland, Miller, Wells, and Barnes, 1946).

From this early work it was apparent that gonorrhoea could be satisfactorily treated by penicillin given orally but, owing to its destruction by the acid in the stomach, the results were less certain than when the parenteral route was used; also the dose required was higher—although not so much higher as had at one time been suggested.

It is important to know that the required dose of antibiotic is in the patient. Many patients with venereal disease cannot be relied upon to take their tablets conscientiously, apart perhaps from one additional dose after leaving the clinic. The fact that gonorrhoea can be cured with but a single injection of penicillin led to a natural preference for injection procedures, and some indeed consider that oral treatment is ill-advised (*Brit. med. J.*, 1957).

With the advent of benzathine penicillin, and the more prolonged penicillinaemia obtained dose for dose by injection than with other parenterally-administered penicillins, it was thought that a single oral dose might be sufficient to cure gonorrhoea. Willcox (1954), however, tried single doses of 0.6 up to 4.8 mega units, and even with 4.8 mega units there were 50 per cent. of failures. When two doses of 2.4 mega units were given 6 hrs apart, there were four failures in 23 patients followed.

The introduction of phenoxymethyl penicillin (penicillin V) provided a preparation less affected by the stomach acid, from the use of which higher peaks and longer duration of penicillinaemia could be obtained dose for dose than with any previously available penicillins. Sheil (1956) described its use in 25 male patients with gonorrhoea who were given 400,000 units thrice daily for 3 days with excellent results (only one relapse and one reinfection). The schedule used, however, was not designed to indicate any potential advantages over single injection methods.

While agreeing that an ineffective oral treatment of gonorrhoea has many disadvantages (*e.g.* fostering of drug-resistant strains of gonococci), it is felt that an effective oral treatment whereby gonorrhoea could be cured by a single dose would be a

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time-saving measure in the clinic. It would have no disadvantages over parenterally-administered penicillin for its administration could be supervised to ensure that the patient received the full amount. Moreover, there is a lower theoretical risk of serious penicillin sensitivity reactions when the oral route is used (Welch, Lewis, Weinstein, and Staffa, 1957).

Present Investigation

The present paper explores the potentialities of phenoxymethyl penicillin in the treatment of acute gonorrhoea with only one or two doses. A total of 85 patients has been treated with 2 or 3 mega units given orally; 33 patients were white and 52 were coloured. As the results were markedly different in the two groups they are considered separately.

White Patients.—The average age of the 33 white patients was 27.1 yrs (extremes 17–62); thirty were single, two were married, and one was separated. Fourteen patients had had no previous venereal incident, but the remaining 19 had had 39 previous attacks of gonorrhoea, seven of non-gonococcal urethritis, and one of epididymitis—an average of 1.4 previous venereal infections each.

The infection had been caught from female strangers (including prostitutes) in fifteen cases, from a friend in thirteen, and from a male in one, while four patients denied exposure. The disease was thus contracted from a stranger in 45.6 per cent. of cases.

The apparent incubation period was 1 to 3 days in eleven, 4 to 7 days in eleven, 8 to 14 days in four, and not known in seven.

The urethral discharge had been present before treatment for 1 to 3 days in 29, 4 to 7 days in two, and over 7 days in two. Twenty patients complained of some dysuria and thirteen did not. The Wassermann reaction and VDRL (or Kahn) test were negative in all. The gonococcal complement-fixation test was performed on sera from 26 patients and gave negative results in 22, a doubtful result in

three, and a positive result in one. The follow-up and results are shown in Table I.

Thus, of 33 patients treated, 27 were followed-up and there were no definite relapses. Four cases of suspected re-infection occurred within 3 months of post-treatment observation (the period after which followed-up patients were discharged as cured). In two of these cases (treated with 3 mega units in one and two doses respectively) the re-infection was noted at 8 to 14 days, and in two cases after this time.

Thirteen patients had received 2 mega units, given in one dose in seven cases, and in two doses (each of one mega unit 6 hrs apart) in six cases; twenty had received 3 mega units, given in one dose in thirteen cases, and in two doses in seven cases. The results are summarized in Table II.

TABLE II
RESULTS OBTAINED BY DIFFERENT SCHEDULES IN WHITE PATIENTS

Schedule		No. Treated	No. Followed	Failure*	Re-infection*	Non-Gonococcal Infection*
Mega units	No. of Doses					
2	single	7	6	—	—	—
3	single	13	9	—	2	1
2	double	6	6	—	—	1
3	double	7	6	—	2	1
Totals		33	27	—	4	3
Percentage of Those Followed		—	100	—	14.8	11.1

* Within 3 months of observation

The overall results in this small series (no definite failures and only 14.8 per cent. of re-infections within 3 post-treatment months) were thus good—at least as good as could be obtained with injection procedures. The results were not materially different whether 2 or 3 million units had been given, or whether single-dose or double-dose schedules had been employed.

Coloured Patients.—Of the 52 Negro patients, 49 were from the West Indies and three from West Africa. The average age was 26.5 yrs (extremes 18–40); 39 were single and thirteen were married. Fourteen had had no previous venereal infection, but the remaining 38 had had 81 attacks of gonorrhoea and fourteen of non-gonococcal urethritis—average 1.8 previous venereal infections each.

The infection had been caught from a stranger in 41 cases, from a friend in nine, and from the wife in one, and one denied exposure. The disease was thus contracted from a stranger in 78.8 per cent. of cases. The apparent incubation period was 1 to 3 days in 29, 4 to 7 days in fourteen, 8 to 14 days in five, over 14 days in two, and not known in two.

TABLE I
RESULTS OF TREATING 33 WHITE PATIENTS WITH 2-3 MEGA UNITS PENICILLIN V ORALLY IN ONE OR TWO DOSES

Follow-up (days)	No. Followed	Satisfactory	Failure	Re-infection	Non-Gonococcal Infection
0	33	—	—	—	—
1-3	27	3	—	—	—
4-7	24	5	—	—	—
8-14	19	4	—	2	—
15-21	13	—	—	—	2
22-28	11	—	—	1	1
30-60	9	2	—	—	—
60-90	7	1	—	1	—
Over 90	5	1	—	3	1

The urethral discharge had been present before treatment for 1 to 3 days in 43, for 4 to 7 days in eight, and for over 7 days in one. 35 patients reported some dysuria and seventeen did not. The Wassermann reaction and VDRL (or Kahn) test were positive in two, the Wassermann reaction was negative but the VDRL test had some reactivity—doubtless in a number of instances due to past yaws—in fifteen, and both tests were negative in 35. The gonococcal complement-fixation test was made on sera from 39 patients and gave negative results in 32, a doubtful result in four, and a positive result in three. The follow-up and results are shown in Table III.

TABLE III

RESULTS OF TREATING 52 COLOURED PATIENTS WITH 2-3 MEGA UNITS OF PENICILLIN V ORALLY IN ONE OR TWO DOSES

Follow-up (days)	No. Followed	Satisfactory	Failure	Re-infection	Non-Gonococcal Infection
0	52	—	—	—	—
1-3	49	6	4	—	—
4-7	39	8	7	1	—
8-14	23	1	2	2	1
15-21	17	—	1	1	—
22-28	15	1	—	—	1
30-60	13	3	—	2	1
60-90	7	3	—	—	—
Over 90	4	1	—	3	—

Thus, of 52 patients treated, 49 were followed-up, and fourteen suspected relapses and six suspected re-infections were noted during the first 3 months of observation. Eleven of the fourteen relapses were noted within 7 days, and thirteen within 2 weeks. Only one of the six suspected re-infections was noted during the first week.

26 patients had received 2 mega units, given in one dose in fourteen cases and in two doses in twelve cases. 26 had received 3 mega units, given in one dose in nine cases and in two doses in seventeen cases. The results are summarized in Table IV.

The overall results in this series were therefore indifferent. The best results were apparently obtained with the schedule employing the highest initial dose (3 mega units) and the worst with the lowest initial dose (one mega unit in the schedule of 2 mega units in two doses).

Comparison of Results in White and Coloured Patients

The differences noted between the white and coloured patients are striking. A similar trend was observed in a London series of gonorrhoea patients treated with 600,000 units of procaine penicillin in one or two daily injections during the period that the penicillin V trial was being undertaken. Neither is the trend confined to penicillin therapy, for it was also noted in a series treated in 1956 (Willcox, 1957) with single injections of 0.5–1.0 g. streptomycin (Table V, opposite).

Penicillin V was as good as penicillin by injection and streptomycin in white patients, but significantly less so in coloured patients. It is noted that the marked difference in the results in the two groups is occasioned by the suspected failures rather than the suspected re-infections, and that the suspected failures occurred nearly three times more frequently in coloured persons.

The reasons for the racial difference are not clear. Social differences in behaviour, in so far as coloured patients may return to the same sexual environment sooner than white patients—before the consort has been secured for treatment—with subsequent re-infection, is one possible reason, although the data presented do not support this view. The decreasing sensitivity of the gonococcus to antibiotics is another.

"Resistance" of the gonococcus to penicillin, still a laboratory phenomenon rather than a clinical problem as far as absolute resistance is concerned, is a developing rather than an initial characteristic (with the sulphonamides there was a large element of initial resistance). It is not known whether the

TABLE IV
RESULTS OF DIFFERENT SCHEDULES IN COLOURED PATIENTS

Schedule		No. Treated	No. Followed	Non-Gonococcal Infection*	Re-infection*	Failure*	Percentage Failures of those Followed
Mega units	Dose						
2	single	14	14	—	2	4	28.6
3	single	9	8	1	1	1	12.5
2	double	12	10	—	1	5	50.0
3	double	17	17	2	2	4	23.5
Totals		52	49	3	6	14	28.6
Percentage of Those Followed		—	100	6.1	12.2	28.6	28.6

*Within 3 months of post-treatment observation.

TABLE V
COMPARISON OF THREE SCHEDULES IN WHITE AND COLOURED PATIENTS

Race	Drug	No. Treated	No. Followed	Non-Gonococcal Infection	Re-infection	Failure	Percentage Failures and Re-infections
White	Penicillin V by Mouth	33	27	3	4	—	11·1
	Procaine Penicillin by Injection	71	53	5	2	3	9·4
	Streptomycin	60	49	13	4	6	12·2
	Total	164	129	21	10	9	14·7
	Percentage of Those Followed	—	100	16·3	7·8	6·9	14·7
Coloured	Penicillin V by Mouth	52	49	3	6	14	40·8
	Procaine Penicillin by Injection	81	63	7	3	10	20·6
	Streptomycin	49	39	5	2	7	23·1
	Total	182	151	15	11	31	27·8
	Percentage of Those Followed	—	100	9·9	7·3	20·5	27·8

gonococcus is developing new metabolic processes or whether the phenomenon is a result of selective breeding of less susceptible strains—as seems more likely. This being the case, resistance is likely to develop slowly especially as a result of passage in a closed community as has happened with the staphylococcus. Hospital staphylococci have a sensitivity pattern to antibiotics quite different from that of “street” staphylococci. It is possible that the same phenomenon is occurring, but in a less marked way with the gonococcus. The consorts of coloured patients in Great Britain represent to some extent a partially “closed” population if the widely-held opinion, that once a white girl consorts with coloured men she is likely to continue to do so, has any meaning. The picture is likely to be blurred by the proportion of “repeater” white patients who are infected again and again from prostitutes in whom the same events may be occurring.

Cost of Treatment with Penicillin V

It has been shown that gonorrhoea can be cured in white patients as efficiently by single oral doses of 3 mega units penicillin V as by injection. This method is likely to prove useful for the relatively few patients who cannot tolerate injections and in circumstances where doctors are consulted away from their syringes. The cost of such treatment, however, makes it prohibitive for routine use at the present time.

For 3 mega units of procaine penicillin hospitals pay only 3s. 9d.—i.e. 9d. for 600,000 units by injection. Tablets of 200,000 units of penicillin V cost £18 per 1,000, or nearly 5s. 5d. for 3 mega units.

Summary and Conclusions

(1) The results of treating 85 patients with acute gonorrhoea with 2–3 mega units phenoxymethyl penicillin (penicillin V) given in one or two doses, have been outlined. In white patients the results have been as good as those obtained with 600,000 units of procaine penicillin in one or two doses, or with single doses of 0·5–1·0 g. streptomycin, both given by injection.

(2) The results of treatment with penicillin V in coloured patients were not good and were worse than the other methods listed. Fourteen suspected failures and six suspected re-infections were noted in 49 coloured persons followed-up, as compared with no failures and four suspected re-infections in 27 white persons followed-up. Possible reasons for this difference, which has also been noted in patients treated with penicillin by injection and with streptomycin, are discussed.

(3) In view of the racial differences, the evaluation of various methods of treating gonorrhoea is becoming increasingly difficult. It is certainly necessary to consider the results of treatment in coloured and white patients separately.

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